Title
Reefer to the Rescue: The Dope on Cannabidiol as a Multi-Symptom Panacea for Dravet Syndrome

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Reefer to the Rescue: The Dope on Cannabidiol as a Multi-symptom panacea for Dravet Syndrome

Cannabidiol Attenuates Seizures and Social Deficits in a Mouse Model of Dravet Syndrome.
Worldwide medicinal use of cannabis is rapidly escalating, despite limited evidence of its efficacy from preclinical and clinical studies. Here we show that cannabidiol (CBD) effectively reduced seizures and autistic-like social deficits in a well-validated mouse genetic model of Dravet syndrome (DS), a severe childhood epilepsy disorder caused by loss-of-function mutations in the brain voltage-gated sodium channel NaV1.1. The duration and severity of thermally induced seizures and the frequency of spontaneous seizures were substantially decreased. Treatment with lower doses of CBD also improved autistic-like social interaction deficits in DS mice. Phenotypic rescue was associated with restoration of the excitability of inhibitory interneurons in the hippocampal dentate gyrus, an important area for seizure propagation. Reduced excitability of dentate granule neurons in response to strong depolarizing stimuli was also observed. The beneficial effects of CBD on inhibitory neurotransmission were mimicked and occluded by an antagonist of GPR55, suggesting that therapeutic effects of CBD are mediated through this lipid-activated G protein-coupled receptor. Our results provide critical preclinical evidence supporting treatment of epilepsy and autistic like behaviors linked to DS with CBD. We also introduce antagonism of GPR55 as a potential therapeutic approach by illustrating its beneficial effects in DS mice. Our study provides essential preclinical evidence needed to build a sound scientific basis for increased medicinal use of CBD.

Commentary
Dravet syndrome (DS) is a debilitating developmental disorder typified by severe seizures and delayed onset of psychomotor deficits. The symptoms start within the first year of life with prolonged, febrile and afebrile generalized seizures in children with no overt developmental disabilities and progress to severe and often refractory epileptic encephalopathy; seizures decrease in frequency and severity with sexual maturity (1, 2). In addition to increasing the risk for sudden unexpected death in epilepsy (SUDEP), the medically refractory status epilepticus in DS can be life-threatening, which makes it crucial to identify drugs to reduce seizures. Additionally, the delayed social and cognitive development and movement disorders that persist even after the seizures abate contribute to long-term morbidity in DS. The quest for a viable drug to limit seizures in DS has intersected with the recent excitement over the potential use of cannabinoids as antiepileptic agents, leading to extensive anecdotal reports of the potential for cannabinoids to limit seizures in DS (3, 4).

Cannabinoids are active derivatives of the marijuana plant, Cannabis sativa. While Δ⁹-tetrahydrocannabinol acting through the cannabinoid receptor type 1 (CB₁R) contributes to the psychoactive effects of marijuana, cannabidiol (CBD) is a nonpsychoactive cannabinoid that has been proposed to limit seizures (4, 5). CBD has low affinity for classic cannabinoid receptors; rather, it blocks signaling through the recently “deorphanized” cannabinoid-related G-protein receptor 55 (GPR55) (6). CBD is promiscuous and, at nanomolar to millimolar concentrations, targets several classes of transient receptor potential channels, including thermosensitive subtypes, enzymes involved in energy and endocannabinoid metabolism and sodium channel subtypes (5, 7, 8). While the anecdotal reports and emerging evidence of beneficial effects of CBD in DS are intriguing (9), preclinical validation of this effect is lacking. Moreover, given the multiple targets of CBD, identifying the mechanisms underlying the beneficial effects of CBD in DS can guide dosing strategies to maximize the therapeutic potential while limiting adverse outcomes.

In a majority of cases, mutations in the sodium channel gene SCN1A form the genetic basis for DS (2). Scn1a⁺/− mice phenocopy human DS, exhibit both thermally induced and spontaneous seizures, and develop autism-like social deficits, which makes them an excellent model to study the mechanisms and therapeutic options in DS (10). The loss of function in Nav1.1 channels in Scn1a⁺/− mice selectively reduces sodium current and excitatory drive in GABAergic interneurons contributing to epileptogenesis. The study by Kaplan and colleagues...
(1) effectively uses the Scn1a<sup>−/−</sup> DS model to shed light on the therapeutic potential for CBD and the synaptic and receptor mechanisms involved.

The study reveals a strong preclinical basis for the use of CBD in DS. They find that CBD pre-treatment reduces both duration and severity of thermally-induced behavioral seizures. Similarly, DS mice examined at 3-4 weeks of age, when spontaneous seizures peak, showed a striking reduction in seizure frequency 4 hours following high dose CBD treatment. Additionally, CBD treatment improved deficits in social interactions, reduced defensive escapes and reduced increases in locomotion observed in DS mice. Curiously, only low dose CBD (<50 mg/kg) improved social interactions whereas considerably higher doses (>100 mg/kg) were required to limit seizures and hypermobility. The effect of CBD on synaptic excitation and inhibition was examined in dentate granule cells in ex vivo slices from DS mice by perfusing CBD at peak brain concentrations observed with high dose CBD treatment. In the presence of glutamate antagonists, CBD increased the frequency of action potential dependent inhibitory postsynaptic currents (IPSCs) in granule cells without altering amplitude or frequency of action potential independent mini-IPSCs. Simultaneously, CBD reduced both spontaneous excitatory postsynaptic currents (sEPSCs) and granule cell excitability. CBD effects on granule cell sEPSCs and excitability were abolished by GABA<sub>A</sub> receptor antagonists suggesting that the effects of CBD on the excitatory circuit are secondary to changes in inhibition. Direct examination of parvalbumin interneurons in non-DS reporter mice, revealed that CBD reduced the minimal current needed to elicit firing (rheobase) and enhanced the rate of firing during suprathreshold current injections, demonstrating that CBD enhances inhibitory interneuron excitability. Mechanistically, although the CB<sub>1</sub>R antagonist enhanced granule cell IPSCs, it did not occlude CBD enhancement of IPSC frequency indicating that CB<sub>1</sub>R receptors are not necessary for CBD action. In contrast, the GPR55 antagonist mimicked the effects of CBD on granule cell IPSCs and excitability and occluded CBD effects on granule cell sIPSCs and interneuron excitability. Together Kaplan and colleagues provide the first preclinical demonstration that CBD treatment could offer acute symptomatic relief in DS. The data show that high-dose CBD acts, in part, by blocking GPR55, which leads to an increase in interneuron excitability.

The demonstration that CBD can suppress both seizure and autism-like symptoms in DS mice is important for the potential clinical utility of CBD to reduce both mortality and morbidity in DS. However, since the study, by design, was restricted to acute drug effects, it would be important to examine whether the effects persist with prolonged use and evaluate the potential for disease modification. The determination that GPR55 signaling contributes to CBD-mediated restoration of synaptic inhibition in DS mice provides valuable insights into the potential mechanism underlying the anticonvulsive effects of CBD. While the study addresses the ability of high-dose CBD to modify network excitability, the processes underlying the effects of low-dose CBD on behavior remain to be determined. The study revealed an exquisite dose specificity of CBD on seizures versus behavior, which is important to consider in a clinical setting. Although different molecular and circuit specific mechanisms likely underlie the high-dose and low dose-effects of CBD, it is conceivable that effects of low-dose CBD on electrical seizures may have been missed due to the exclusive focus on behavioral seizures. GPR55 is expressed in hippocampal glutamatergic terminals where it enhances glutamate release but shows limited expression in GABAergic neurons (7, 1). Whether GPR55 is selectively expressed in parvalbumin interneurons or overlaps CB1 expressing interneurons in the dentate needs to be examined to appreciate the circuit effects of CBD/GPR55 signaling. Still, mechanisms mediating GPR55 modulation of interneuron rheobase and excitability remain to be identified. Although, effect of CBD/GPR55 on action potential threshold was not determined, it is possible that GPR55 could modulate sodium channels as has been reported in recombinant systems (8). Detailed understanding of the molecular underpinning of anticonvulsive and behavioral effects of CBD would be crucial to mitigate DS symptoms while limiting potential off-target effects of CBD.

In conclusion, Kaplan and colleagues provide the first preclinical demonstration that CBD may help alleviate seizures in a mouse model of DS validating the translational potential of CBD in patients with DS. The study identifies GPR55 as a potential target through which CBD transiently reverses the network-level imbalance between synaptic excitation and inhibition observed in DS mice. The exciting finding of dose-dependent effects of CBD on DS symptoms is sure to spur additional studies on the cell-type specificity of GPR55 expression and the functional effectors underlying its modulation of active neuronal properties. The demonstration that CBD improves deficits in social interactions in DS launches an exciting therapeutic possibility of alleviating behavioral impairments that persist beyond the seizures and pave the way for mechanistic studies that could positively impact treatment of autism spectrum disorders.

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References

